REMARKS

Status of the Claims

Claims 32-36, 43-46 and 51-53 were previously pending. Claim 35 and 36 are allowed. Claim 34 has been canceled without prejudice or disclaimer. Claims 54-57 have been added, which incorporate subject matter that the Examiner had indicated is enabled by the specification. Accordingly claims 32-33, 43-46 and 51-57 are pending and at issue.

Acknowledgement of Allowable Subject Matter

Applicants acknowledge with appreciation the finding that claims 35 and 36 are allowable, and that claim 34 would be allowable if rewritten in independent form. Claim 32 has been amended to incorporate the limitation of claim 34. Accordingly, independent claim 32 and dependent claim 33 (which depends from claim 32) contains all the limitations of claim 34 and should stand in condition for allowance.

Rejections Under 35 USC § 112, First Paragraph

Claim 43-46 and 50-53 are rejected as not enabled by the specification. The Examiner admits that the specification is enabling for inducing tolerance to an allogenic transplant antigen in a subject by intravenously administering total cellular RNA or total cellular mRNA prior to the allogenic transplantation, wherein the cells are from the graft tissue or spleen cells.

The Office Action states that "the specification does not reasonably provide enablement for inducing tolerance to an allogenic transplant tissue by intravenous[ly] administering total cellular RNA/mRNA from any cells at any time." Applicants respectfully submit that claim 43 is enabled, and that the Examiner's maintenance of this rejection is based on a misunderstanding of our previous arguments, declarations, and amendments to the claims.

With respect to the timing issue, claim 43 has been amended to recite intraveneously administering RNA which comprises allogenic transplant tissue antigen RNA prior to allogenic transplantation solely to advance prosecution.

With respect to the cell selection, applicants have previously stated that a person of ordinary skill could select cell types which include antigen RNA (see page 5, lines 18-20, of Response filed June 23, 2004). Administering RNA which comprises antigen RNA was previously recited in claim 43. Therefore, the Examiner's statement in the present Office Action that "the claims broadly encompass administering *RNA from any cell and any source, not limited to cells that contain the antigen*" ignores the language of claim 43, which states that antigen RNA is administered. It necessarily follows that antigen RNA is taken from cells which comprise antigen RNA, and that antigen RNA cannot be harvested from cells that do not contain antigen RNA. Therefore Applicants cannot understand the Examiner's current position that the claims are "*not limited to cells that contain the antigen*". Nevertheless, Applicants have specified in amended claim 43 that the RNA is administered from cells which comprise allogenic transplantation antigen RNA.

Applicants note that claim 43 previously recited "wherein the antigen is an allogenic transplant tissue antigen", and the term "antigen RNA" should be interpreted along these lines. In an attempt to clarify the claims, Applicant submitted an informal proposed amendment to claim 43 on November 11, 2004, reciting "intravenously administering RNA from cells which comprise graft tissue antigen RNA". This amendment was consistent with Applicants previously intended claim scope. After reviewing the proposed claims, the Examiner stated in a telephone interview with the undersigned attorney her belief that, as a matter of science, only RNA from graft tissue cells themselves would work, and that claims embracing harvesting *graft tissue* RNA from other cells besides graft tissue cells is too broad and not enabled. The Examiner invited the current Response.

The position taken by the Examiner is not supported by evidence. On the contrary, the experimental evidence of record shows that RNA from spleen cells induces tolerance to transplanted skin grafts (see Third Granstein Declaration, submitted December 12, 2003). This observation directly refutes the Examiner's position. The Examiner's current position that only antigen RNA from the skin grafts themselves would work to elicit tolerance is also inconsistent with her own statement in the present Office Action: RNA from spleen cells is enabled. (See Page 2 of Office Action dated September 23, 2004). RNA from spleen cells containing allogenic transplant tissue RNA is an example of cells from which allogenic transplant tissue antigen RNA can be harvested

besides the transplanted tissue cells themselves. Applicants respectfully sumbit that the Examiner's position, which raises previously settled issues and clearly contradicts data submitted by declaration, is mistaken.

Claim 43 has been amended to recite intravenously administering RNA from cells which comprises allogenic transplant tissue antigen RNA. The term allogenic transplant tissue antigen RNA encompasses *major histocompatibility complex (MHC)* class I and class II antigens. Mismismatching of these antigens from the host and the graft is responsible for allograft rejection. (See also attached text from "Immunology", described below) The present invention relates to the finding that intravenously administering RNA which comprises allogenic transplant tissue antigen RNA (also correctly termed "MHC antigen RNA") induces tolerance to allogenic transplantation rejection, and hence tolerance to the mismatching of allogenic transplant tissue antigen RNA (or "MHC antigen RNA").

RNA from any allogenic tissue which includes RNA (or total messenger RNA) that expresses transplantation antigens would be capable of inducing tolerance to the graft. There is nothing inherent to graft tissue cells that dictates that only RNA sourced from these cells induces tolerance to the transplant graft tissue. Therefore, Applicants respectfully submit that claim 43 is enabled.

In order to advance prosecution, Applicants would agree to amend claim 43 to recite "graft tissue antigen RNA", or "MHC antigen RNA", instead of "allogenic transplant tissue antigen RNA", as these claims all refer to the same antigen, and are all supported by the specification. The specification repeatedly refers to antigen-specific RNA, and states:

> In the tolerization methods and pharmaceutical compositions of the invention, the RNA can be total cellular RNA from tissues containing the antigen, total cellular mRNA from tissues S, or mRNA encoding the antigen. *Preferred antigens include . . . transplant antigens.*

(Specification, page 6, line 21 - 24, emphasis added). Attached as Exhibit A is a copy from the text "Immunology" (copyright 1984) which states that the terms major histocompatibility complex (MHC) class I and MHC class II (or Ia) antigens are subsets of transplantation antigens. Therefore, the specification supports use of the term "MHC antigen" instead of allogenic transplant tissue antigen, should the Examiner find this term more acceptable. This text states that MHC antigens encodes a variety of cell-surface proteins that mediate immune cell-cell interactions and trigger rejection of foreign tissue transplants. This text supports Dr. Granstein's already submitted data with respect to use of RNA from spleen cells that the presence of RNA encoding MHC (or allogenic transplant tissue antigens, as used in the specification) antigens from the transplant tissue is key, not the cellular source of the particular MHC antigen RNA.

New claims 54-57 contain the limitations of claim 43, claim 44 (total cellular RNA) or claim 45 (total cellular mRNA), and specify that the RNA is from cells of the allogenic transplant tissue or spleen cells. Therefore, these claims should stand in immediate condition for allowance based on the subject matter that the Examiner identified in the Office Action as enabled by the specification. As set forth above, however, claim 43 is also enabled by the specification.

Rejections Under 35 USC § 103

Claim 32 stands rejected as obvious over Qui taken with Nair. Claim 33 stands rejected as obvious over Qiu taken with Nair and further in view of Segal. The Examiner has indicated that claim 34 is allowable if rewritten in independent form.

Although Applicants respectfully disagree with these rejections, claim 32 has been amended to incorporate the limitation of claim 34. Claim 33 depends from claim 32, and hence also contains the limitation of allowable claim 34. Applicants request that this rejection be withdrawn.

In view of the above amendment, applicant believes the pending application is in condition for allowance. The Examiner is requested to contact the undersigned if an interview would be helpful in passing this application to issuance.

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Respectfully submitted,

By _____

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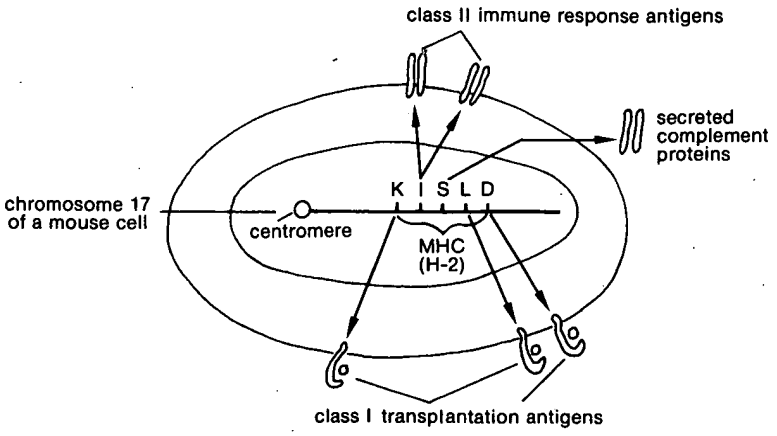

Figure 1-12
Organization of the MHC (H-2 complex) of the mouse. K, D, and L denote loci that code for the class I or transplantation antigens. I denotes a set of loci that codes for the class II or Ia antigens. S designates a region that codes for two or more complement components.

jor class of antibody during the primary response is IgM, whereas IgG is the major class of antibody during the secondary response.

Tolerance

Clonal selection also underlies the phenomenon of *tolerance.* Organisms typically do not mount immune responses against their own macromolecules and are thus said to be tolerant of their own antigenic determinants. Tolerance is created by a process that eliminates or suppresses all clones of lymphocytes that could respond to normal constituents of the organism.

1-5 Gene products of the major histocompatibility complex play a fundamental role in immune responses

The *major histocompatibility complex* (MHC) is a discrete chromosomal region encoding a variety of cell-surface proteins that mediate immune cell-cell interactions and trigger rejection of foreign tissue transplants (Figure 1-12). A subset of the transplantation antigens, called the class I MHC antigens, is present on virtually all cells of a vertebrate organism and appears to play an important role in T-cell surveillance for virally infected cells and cancer cells. Another subset of MHC-encoded proteins, called the class II or Ia (*i*mmune response *a*ssociated) antigens, appears to regulate a number of the cellular interactions involved in immune responses. The MHC also encodes several components of the *complement* pathway, which is an effector mechanism activated by the humoral immune response (Concept 9-2).

These various MHC functions have been found in all vertebrates examined, but only some MHC-like functions have been found in

advanced invertebrates. Thus the emergence of the vertebrate immune system is correlated evolutionarily with that of the MHC. This coincidental appearance is consistent with the fundamental role of the MHC in the differentiation, regulation, and expression of the immune response.

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Problems

1-1 Indicate whether each of the following statements is true or false. Explain the error in each statement you consider to be false.

(a) An antibody molecule has one type of antigen-binding site.
(b) A large antigen can generally combine with many different antibody molecules.
(c) Antigens combine with specific antibodies and stimulate the production of these antibodies.
(d) A hapten can stimulate antibody production but cannot combine with antibody molecules.
(e) In a secondary immune response, IgM is the major class of antibody synthesized.
(f) Immunologic memory can last 20 years or more.
(g) The B-cell receptor molecule has not yet been identified conclusively.
(h) Plasma cells are the major effector cells of the B-cell response; several classes of small lymphocytes are the effector cells of the T-cell response.

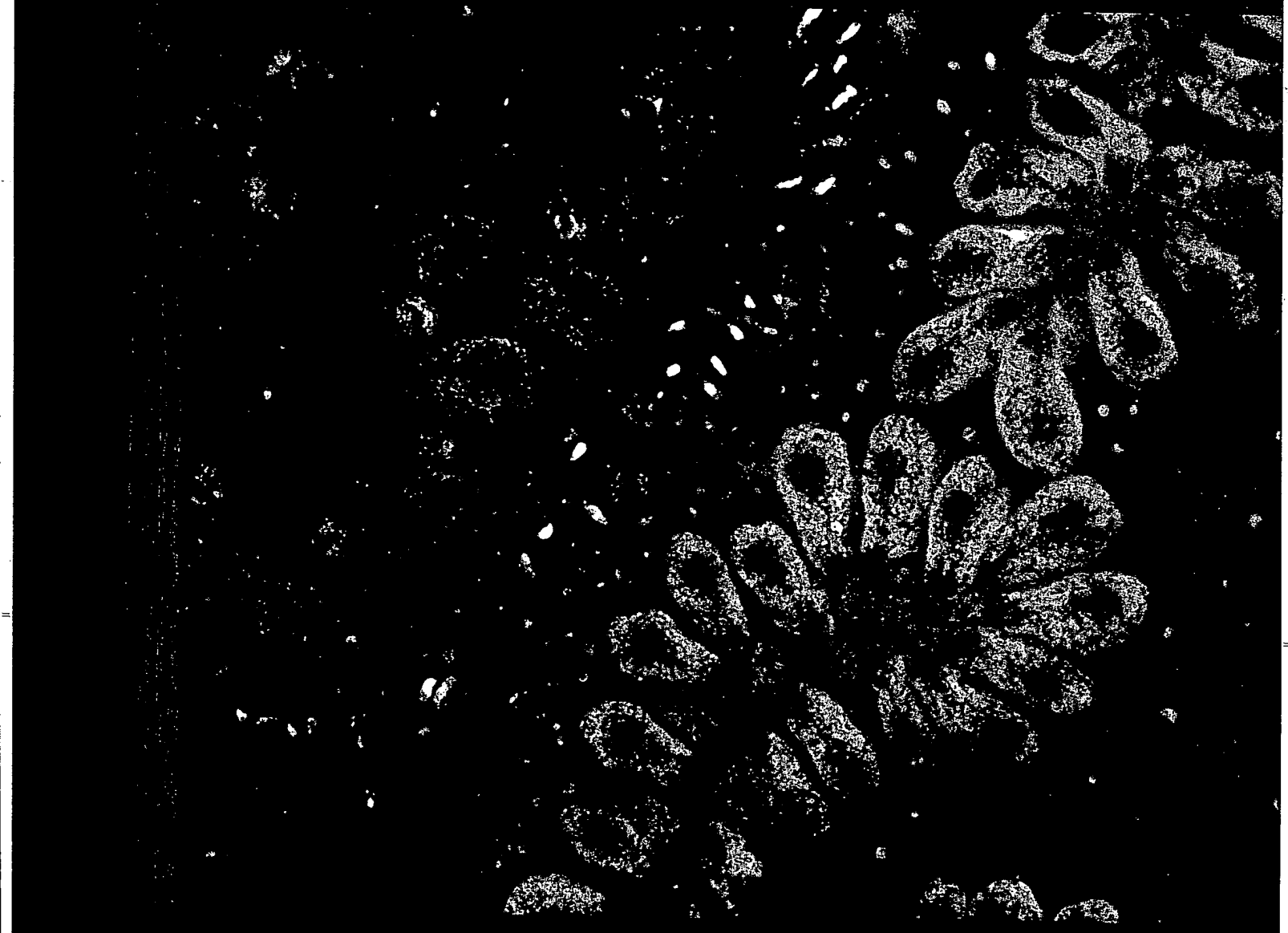
1-2 (a) When haptens are attached to a larger _____ molecule, they become immunogenic.
(b) _____ are the terminal effector cells of B-cell differentiation.
(c) T cells mediate _____ immunity.
(d) The clonal selection theory contends that lymphocytes commit themselves to the synthesis of one type of antibody molecule prior to exposure to _____, but that _____ triggers the final stage of differentiation.
(e) _____ immunity is protective against extracellular bacterial infections.
(f) The presence of specific immunoglobulin response to antigen in the animal kingdom is thought to be limited to _____.

1-3 For each of the following conditions, indicate whether a humoral or a cellular immune response is more effective or relevant.

Immunology

SECOND EDITION

Hood • Weissman
Wood • Wilson



Front Cover:

Natural transplantation in Tunicates

Among some nonvertebrates, such as tunicates, individuals can fuse to form a multi-individual colony. *Colonial tunicates* form colonies by a complex recognition system involving fusion or rejection of extracorporeal blood vessels between two individuals or two colonies. When fused, the two colonies share blood cells. On the cover a colony bearing orange pigment cells (lower right) has fused with a colony bearing purple pigment cells (upper left), resulting in a mixing of the blood cells. Fusion or rejection is genetically controlled in this species by a single gene locus which has many alleles; two individuals must share the same allele to fuse. The same locus (or a closely linked locus) also controls *fertilization* (sperm-egg fusion) between two individuals; in this case sperm and egg must *not* share alleles to fuse.

This type of genetic control of "transplantation" extends into all vertebrates, where a genetic region called the *major histocompatibility complex* (MHC) encodes transplantation antigens (cell-surface glycoproteins) which prevent the acceptance of the type of unnatural transplants tried by transplantation biologists and physicians. The products of the MHC are also used as signals for intercellular communications between immunity cells within an individual, and through these signals control our susceptibility to infections. Because the biology and molecular genetics of the MHC are recurring themes throughout this book, we have chosen this cover to illustrate an example of the unity of important biological principles, including the possibility that tunicate fusion/rejection genes may be forerunners of the vertebrate MHC. (Photo courtesy of Virginia Scofield and Irving Weissman).

Back Cover:

Structure of an Antibody Molecule

This computer graphic representation by Arthur J. Olson illustrates the protein backbone of the human myeloma IgG Dob. This representation is based on the X-ray crystal studies of M. Navia, E. Silverton, V. R. Sarma, G. H. Cohen, and D. R. Davies. The image was produced using software developed by Olson, T. J. O'Donnell, and Michael L. Connolly.

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